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Original

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Ileal perforation and massive intestinal haemorrhage from endometriosis in pregnancy: Case report and literature review

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Short title

Intestinal endometriosis in pregnancy

Condensation

Women with severe endometriosis have potential risks for intestinal perforation and massive intestinal haemorrhage in pregnancy.

Abstract

An increasing number of women with severe endometriosis have conceived through assisted reproductive technology. However, endometriosis can cause life-threatening complications for both the mother and baby during pregnancy. We herein describe a case of endometriosis-induced spontaneous ileal perforation with massive intestinal haemorrhage in a pregnancy that underwent Caesarean section, right hemicolectomy and terminal ileum resection at 33 weeks of gestation. Spontaneous perforation associated with intestinal endometriosis in pregnancy is a rare complication, and only seven cases have been reported in the English literature. To the best of our knowledge, this is the first report of spontaneous ileal perforation due to endometriosis. Moreover, this is probably the first case of massive intestinal haemorrhage in pregnancy that resulted from intestinal endometriosis. These risks must be explained to couples suffering from endometriosis-related infertility prior to conception by assisted reproductive technology, and multidisciplinary management may be mandatory for women with severe endometriosis in pregnancy. (149 words)

Key words

ectopic decidua, endometriosis, ileal perforation, intestinal bleeding, pregnancy

Introduction

Endometriosis is associated with subfertility, with a prevalence of about 10 to 15% of reproductive-age women (1). Today, an increasing number of women with endometriosis can achieve pregnancy through assisted reproduction technology (ART). Endometriosis is a risk of adverse pregnancy outcome, including preterm birth and antepartum haemorrhage (2). Moreover, endometriosis can cause rare but potentially life-threatening complications for both the mother and baby, such as spontaneous haemoperitoneum (3), and intestinal perforation (4).

We present a case of pregnancy complicated by endometriosis that resulted in spontaneous ileal perforation and massive intestinal haemorrhage. The patient required Caesarean delivery along with right hemicolectomy and terminal ileum resection at 33 weeks of gestation. This report is believed to be the first case of spontaneous ileal perforation and the first case of massive intestinal haemorrhage in pregnancy from intestinal endometriosis. We also review all cases of intestinal

perforation in pregnancy due to endometriosis that have been reported in the English literature.

Case Report

A 38-year-old Japanese nulliparous woman was admitted to our hospital because of persistent upper right abdominal pain at 28 weeks plus four days gestation. She had a history of dysmenorrhoea and infertility due to endometriosis. She underwent a laparotomy excision of an endometriotic cyst of the right ovary when she was 23 years-old and bilateral salpingectomy for haematosalpinx when she was 36 years-old. Preoperative magnetic resonance imaging (MRI) and the second operative findings showed severe adhesions involving the uterus, bladder, and intestine (Figure 1). After the second operation, she conceived through *in vitro* fertilisation (IVF). Upon admission, her temperature was 36.9°C, her blood pressure was 110/62 mmHg, and her pulse was 72 beats per minute. Physical examination showed mild focal tenderness in the right lower quadrant without guarding or rebound tenderness. Laboratory data were: white blood cell (WBC) count, 22,300/ μ l and C-reactive protein (CRP), 14.6 mg/dl (normal, ≤ 0.2 mg/dl). MRI revealed fat

stranding in the ileocaecal region suggestive of periappendiceal inflammatory changes (Figure 2A), but did not show an enlarged appendix. The entire anterior surface of the uterus seemed to be covered by the bladder (Figure 2B). Antibiotic (Ceftriaxone) treatment was started for suspected appendicitis. WBC count and CRP normalised in accordance with the improvement of clinical symptoms. She had an uneventful course until 33 weeks of gestation, when her WBC count and CRP started to elevate gradually up to a WBC count of 10,300/ μ l and CRP of 6.2 mg/dl. The patient experienced a recurrence of abdominal pain. These symptoms persisted despite the reinitiation of antibiotic treatment (Ceftriaxone). Moreover, intermittent melena occurred at 33 weeks and five days of gestation. Thus, Caesarean section was performed on that day. Since the anterior and posterior bladder walls were extensively adhered to the anterior abdominal wall and anterior uterine wall, respectively, we incidentally entered the cavity of the bladder while entering the peritoneal cavity (Figure 3A). After consultation with expert urologists, the posterior bladder wall was also incised before an incision was made into the uterus, and a 2356g healthy male infant was delivered through the bladder intentionally. Surgeons in gastroenterology conducted adhesiolysis of severe adhesions involving the uterus,

the sigmoid colon, the ascending colon, the appendix, the caecum, and the ileum. The adhesiolysis revealed terminal ileal perforation with abscess formation (Figure 3B) and a normal appearance appendix. During the operation, the patient unexpectedly developed acute profuse melena, and gastroenterologists performed lower gastrointestinal endoscopy during laparotomy (Figure 3C). The endoscopic exam showed massive intestinal haemorrhage, but did not detect active bleeding sites in the rectum, colon, and terminal ileum; however, a reddish-brown protruding spot with small erosions was observed in a few places. Right hemicolectomy and terminal ileum resection was performed. The length of the residual small bowel was approximately 300 cm. The total amount of blood loss including amniotic fluid was 5100 g, and 12 units of red blood cells and 9 units of fresh frozen plasma were administered. *Citrobacter freundii*, *Enterobacter cloacae*, and *Enterococcus faecium* were detected in the abscess culture. The patient had a prolonged postoperative course complicated by paralytic bowel obstruction and ventral incisional hernia. The infant was discharged without complications, and the patient was discharged on postpartum day 57.

Surgical specimens showed a terminal ileal perforation with ileal stenosis

observed in the 4 cm anal side from the site of the perforation. Histopathological examination revealed intestinal endometriosis with stromal decidual changes that widely affected the distal ileum (Figure 4A), the appendix, the caecum, and the ascending colon. Decidualised stroma with endometrial glands were mainly extended from the subserosa to the intestinal submucosa. Neutrophil infiltration was observed in the intestinal mucosa at the site of the ileal perforation (Figure 4B).

Discussion

Intestinal endometriosis affects 3.8% to 37% of the patients with a diagnosis of endometriosis (5). The most frequent location of intestinal involvement with endometriosis is the sigmoid colon, followed by the rectum, the ileum, the appendix, and the caecum (5). Intestinal endometriosis is defined as infiltration of endometrial-like glands and stroma reaching at least the subserous fat tissue or adjacent to the neurovascular branches (5). Endometrial glands and stroma are found invading the intestinal wall from the serosa inward, but the submucosa is rarely involved in endometriosis. Thus, intestinal perforation linked to endometriosis is quite rare, and there were only nine cases of intestinal perforation due to

endometriosis that were not associated with pregnancy in the English literature (4).

In pregnancy, ectopic decidua, which is induced primarily by progesterone, can occur by *de novo* development from the superficial celomic stroma or by the transformation of a pre-existing endometriosis. Spontaneous intestinal perforation due to ectopic decidua is a rare complication, as only seven (4, 6-11) cases have been reported in the English literature (Table 1); the locations of perforations were the sigmoid colon ($n = 3$), the appendix ($n = 3$), and the rectum ($n = 1$). The present case is the first report of spontaneous perforation of the ileum due to ectopic decidua. Peritonitis during pregnancy is associated with high maternal and foetal mortality. The previous seven cases needed prompt surgical intervention. Fortunately, severe pelvic adhesions in this case confined the abscess to a localised area, and led to successful continuation of pregnancy for a further five weeks.

In the current case, a preoperative diagnosis of ileal perforation was almost impossible because of a lack of clinical features suggestive of intestinal perforation. Intestinal perforation was suspected in Cases 1 and 5 (sigmoid colon perforation) and in Case 7 (rectal perforation) because a radiograph revealed free air in the peritoneal cavity with the patients' deteriorating clinical condition. Case 4 underwent an

emergency operation due to foetal distress, leading to the diagnosis of perforation of the sigmoid colon. In Cases 2, 3 and 6, appendectomy was performed with a diagnosis of acute appendicitis. Perforation of an area of the bowel other than the appendix seems to require pregnancy termination through Caesarean section followed by additional surgery, such as resection of the sigmoid colon, although it should be considered whether continuation of the pregnancy is possible in the early second trimester.

Pre-existing endometriosis-derived ectopic decidua is very similar to *de novo* ectopic decidua. A past history of endometriosis and the presence of glandular endometrial structures can aid in differentiation. *De novo* ectopic decidua is usually asymptomatic and found incidentally during Caesarean section, mostly on ovarian surfaces or the uterine serosa. It also presents on the appendix, omentum, and peritoneum, etc. (3). Perforation of the appendix in Cases 2 and 6 might have arisen from *de novo* ectopic decidua, because there was no apparent history of endometriosis and no apparent endometrial-like glands in the decidualised stroma. In contrast, the current case had a history of severe endometriosis. Moreover, endometrial glands with decidualised stroma were observed in the submucosa,

suggesting that the pathogenesis of ectopic decidua was attributed to a pre-existing endometriosis. Intriguingly, Cases 3 to 5 had no history of endometriosis and no other apparent findings of pelvic endometriosis upon operation. However, intestinal perforation occurred unexpectedly and endometrial glands in decidualised stroma were identified. These three cases are probably due to isolated intestinal endometriosis. Intestinal endometriosis generally coexists with other pelvic involvement, but occurs without extra-intestinal involvement in 0.88% of patients with histologically proven intestinal endometriosis (12). A review of the previous seven cases suggests that intestinal perforation can occur despite the pathogenesis of ectopic decidua.

Although it is unclear whether pregnancy itself is a risk factor for intestinal perforation, the enlarged uterus on the strictly adherent intestine and the decidualised and weakened part of intestinal endometriosis are likely to increase the risk for intestinal perforation. Moreover, constipation is common in pregnancy, so the intestinal stenosis due to endometriosis may cause an increase in intra-intestinal pressure and subsequent intestinal perforation, although the patient experienced relatively loose stools once a day before admission.

Because ectopic decidua is highly vascularised, it can cause massive haemorrhage during pregnancy (3). Indeed, dozens of cases of fatal intra-peritoneal haemorrhage have been reported, but there was only one previous report that presented intestinal haemorrhage by ectopic decidua (13). Bashir showed massive haemorrhage caused by decidualisation of the mucosal surfaces of the ileum, the caecum and the ascending colon, resulting in foetal demise at 20 weeks of gestation (13). Bashir stated that the intestinal haemorrhage was attributed to *de novo* ectopic decidua rather than pre-existing endometriosis, because the case had no endometrial glands in decidualised stroma. The current case had endometrial glands and decidualised stroma involving the submucosa of the ileum, the appendix, the caecum, and the ascending colon. Thus, pre-existing endometriosis seems a probable cause of intestinal bleeding. Although intestinal endometriosis extending to the submucosa is quite rare, intestinal endometriosis should be considered a potential cause of intestinal bleeding in pregnancy.

In conclusion, severe endometriosis can cause fatal complications such as intestinal perforation or massive intestinal bleeding. These risks must be explained to couples suffering from endometriosis-related infertility prior to conception by ART,

and multidisciplinary management may be mandatory for women with severe endometriosis in pregnancy.

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Figure Legends

Figure 1. Dense adhesions between the uterus and its surrounding structures before conception.

Preoperative sagittal T2-weighted MR image before the second operation (left) and the intraoperative view of severe adhesions around the uterus (right). Arrow indicates the uterine fundus buried in adhesions. Both the anterior cul-de-sac (arrowhead) and the Douglas pouch (double arrowhead) are completely closed due to dense adhesions.

Figure 2. T2-weighted MR image at 28 weeks of gestation.

(A) T2 weighted MR images showing fat stranding around the ileocaecal region suggestive of peri-appendiceal inflammatory changes (left, arrow), and normal appearance of the appendix (right, arrow). (B) T2 weighted sagittal MR image

showing that the fundus of the bladder is stretched upward to the uterine fundus (arrow).

Figure 3. Intraoperative views.

(A) The posterior wall of the bladder covering the surface of the anterior wall of the uterus. The bladder cavity was opened, and indwelling urinary catheter was seen (arrow). The fundus of the bladder (arrowhead) is stretched upward to the uterine funds. (B) Abscess formation around the terminal ileum. Adhesiolysis revealed abscess formation in a confined space formed by severe adhesions involving the posterior uterine wall (arrowhead), ascending colon (arrow), appendix, caecum, and ileum (double arrow). (C) Endoscopic image of the sigmoid colon. Massive intestinal haemorrhage (left) and a protruding spot with a small erosion (right) were observed.

Figure 4. Histology of ileum adjacent to area of perforation. (A) Decidualised endometrial stroma with endometrial glands in the submucosa (magnification; x 20 and x 100). (B) Marked neutrophil infiltration near the site of perforation (magnification; x 20).

Disclosure

The authors report no conflict of interest.

Table 1. Intestinal perforation from ectopic decidua in pregnancy.

Case	Author	Year	Age, years	Gravity/Parity	Onset, weeks of gestation	Presenting symptoms	Site of perforation	History of endometriosis	Adhesion, other endometriosis	Presence of glandular endometrial structures	Gestational weeks at delivery	Mode of delivery	Surgery
1	Clement (6)	1977	28	0/0	37	Crampy lower abdominal pain and mucus discharge per rectum	Sigmoid colon	Yes	None, none	Yes	37	Vaginal delivery following surgery	Segmental resection of the sigmoid colon with end sigmoid colostomy
2	Gini (7)	1981	23	1/0	35	Right lower abdominal pain	Appendix	N/A	None, none	N/A	35	Caesarean	Appendectomy
3	Nakatani (8)	1987	25	2/0	26	Nausea, vomiting, and abdominal pain	Appendix	None	Yes, none	Yes	Full-term	Vaginal	Appendectomy
4	Loverro (9)	1999	28	1/1	35	Crampy lower abdominal pain and hyperpyrexia	Sigmoid colon	None	Yes, N/A	Yes	35	Caesarean	Segmental resection of the sigmoid colon with end sigmoid colostomy
5	Schweitzer (10)	2006	32	0/0	40	Abdominal pain and dyspnoea	Sigmoid colon	None	None, none	Yes	40	Caesarean	Segmental resection of the sigmoid colon with end sigmoid colostomy
6	Faucheron (11)	2008	28	N/A	27	Right sided abdominal pain and nausea	Appendix	N/A	N/A, N/A	N/A	Full-term	Vaginal	Appendectomy
7	Pisanu (4)	2010	37	N/A	33	Sepsis, abdominal pain and hyperpyrexia	Rectum	Yes	Yes, N/A	N/A	33	Caesarean	Hartmann operation and appendectomy
8	Nishikawa (present case)	2012	38	0/0	28	Upper right abdominal pain	Ileum	Yes	Yes, Yes	Yes	33	Caesarean	Right hemicolectomy and terminal ileum resection

N/A: not available.

Figure 1

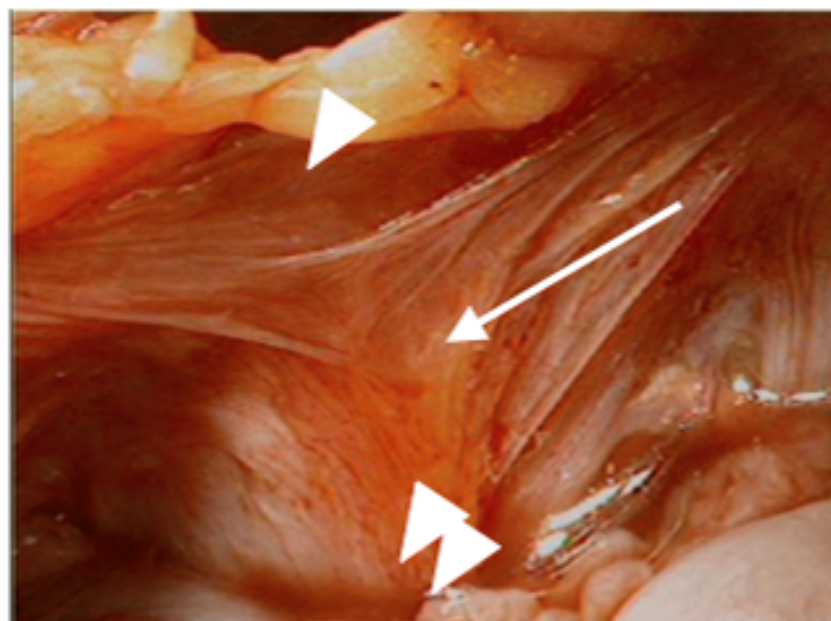
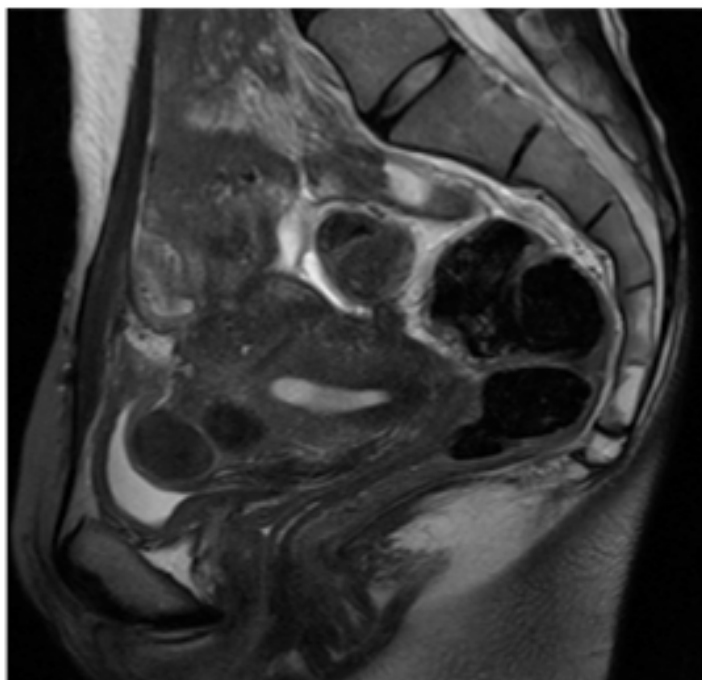
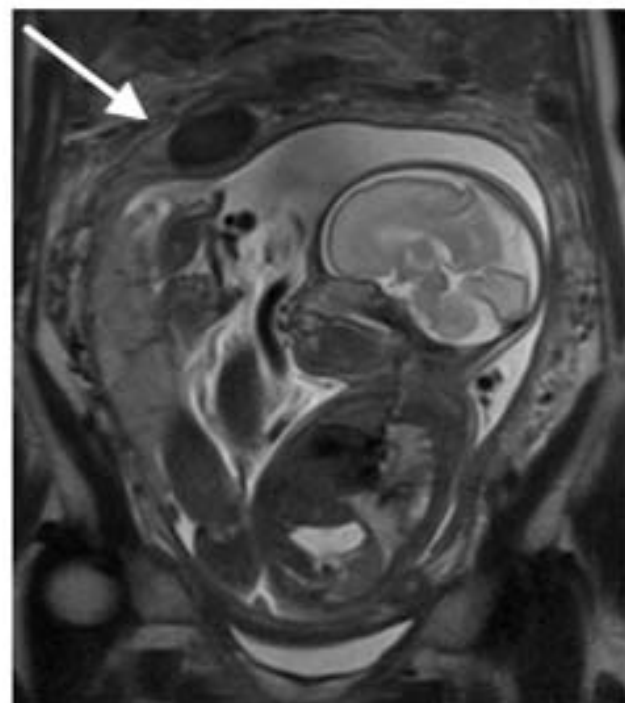
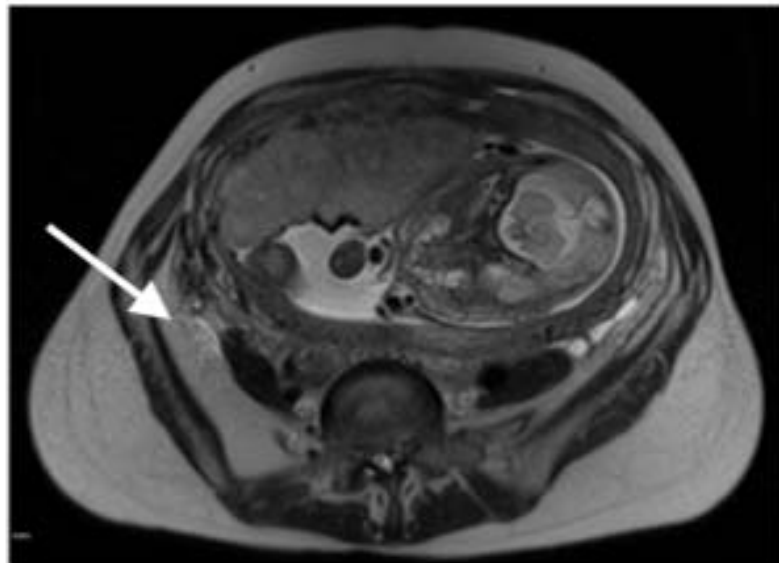


Figure 2

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B

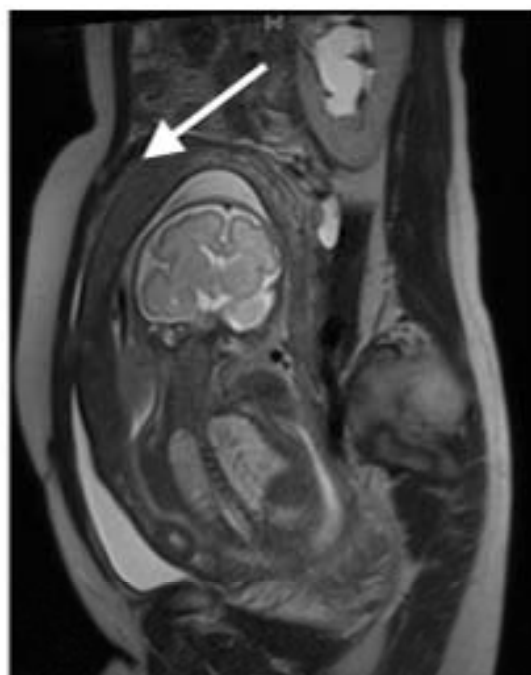
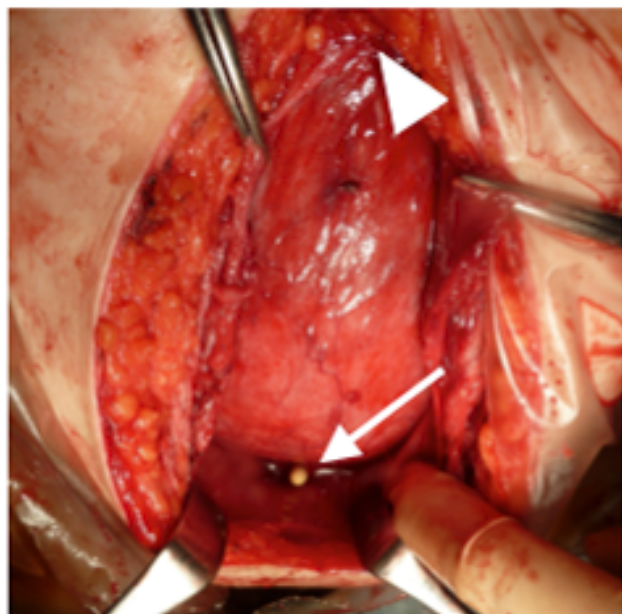
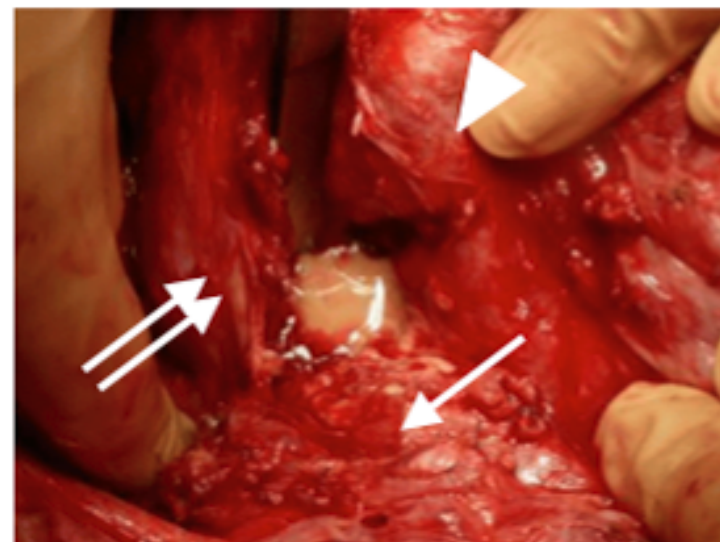


Figure 3

A



B



C

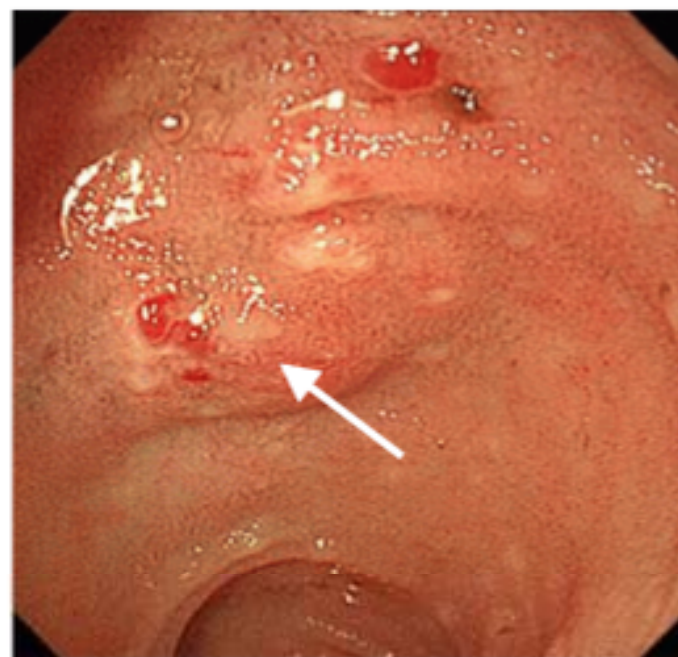
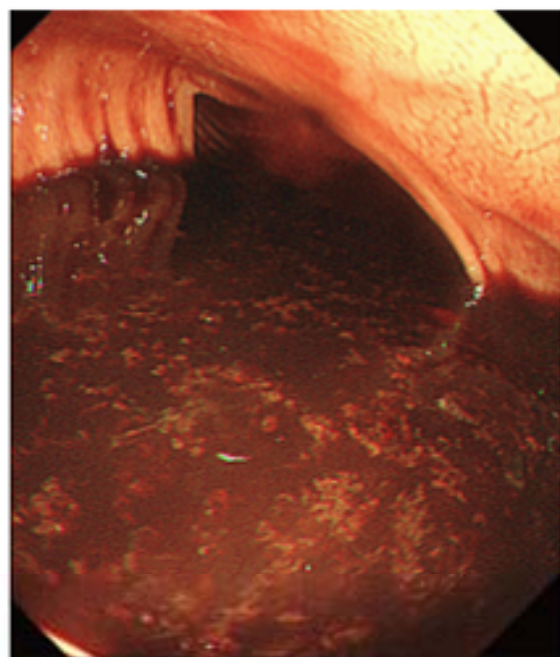
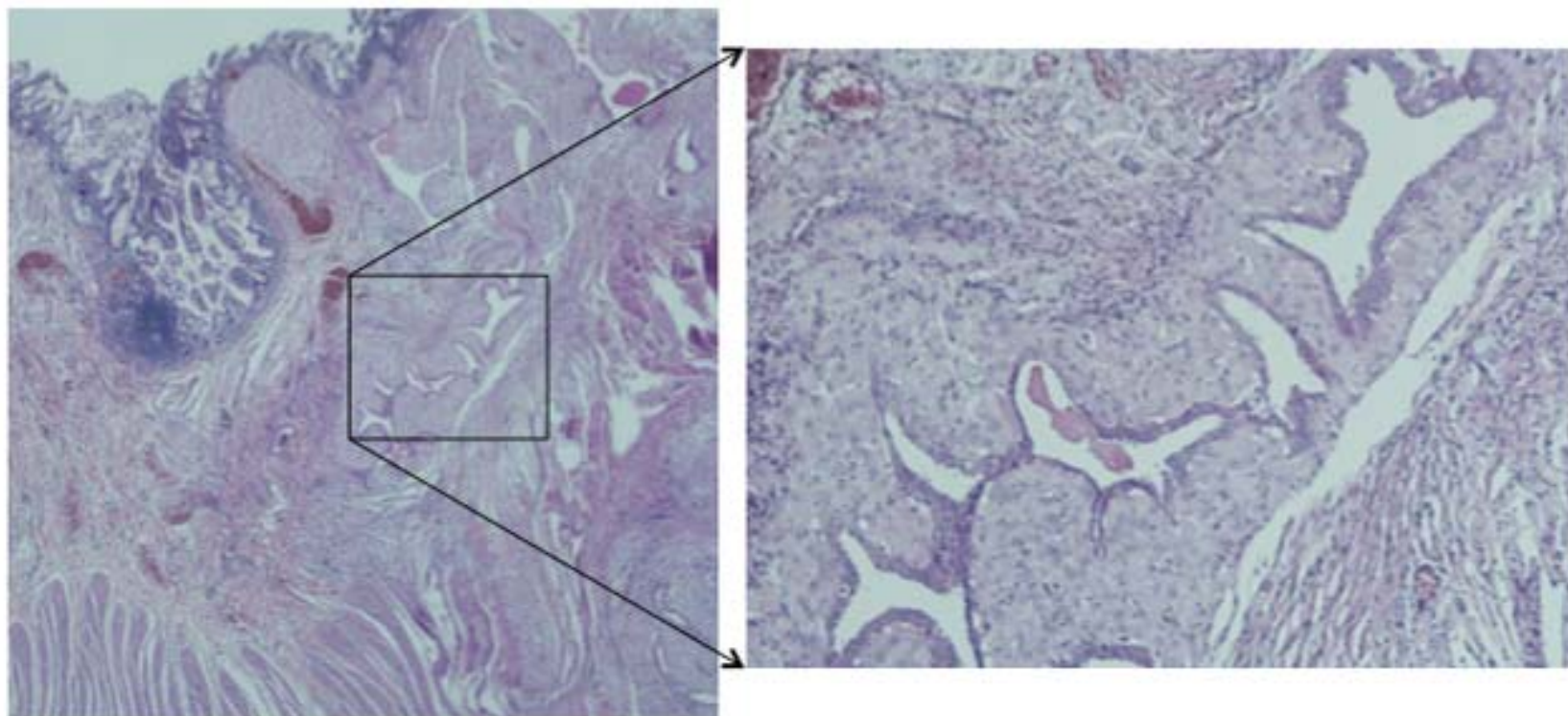


Figure 4

A



B

